DISEASE MODIFYING TREATMENT USE AND FACTORS RELATED TO PROGNOSIS IN MULTIPLE SCLEROSIS: A FIVE-YEAR FOLLOW-UP AT THE UNIVERSITY HOSPITAL OF TAMPERE, FINLAND FROM 2010 TO 2014

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JOHANNA VUORIO: Taudinkulkua muokkaavan lääkityksen käyttö ja MS-taudin ennusteeseen vaikuttavat tekijät: Viiden vuoden seuranta Tampereen yliopistollisessa sairaalassa vuosina 2010-2014.

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Avainsanat: multiple sclerosis, relapsing-remitting MS (RRMS), primary progressive MS (PPMS), progression, short term outcome, prognosis, predictive factors, incidence

Multippeliskleroosi eli MS-tauti on Suomessa nuorten aikuisten yleisin invalidisoiva keskushermoston sairaus ja yleisin demyelinaatiosairaus. Tässä tutkimuksessa selvitettiin MS-tapausten ilmaantuvuutta Tampereen Yliopistollisessa sairaalassa vuosina 2010-2014 ja ennustekijöitä taudin etenemiselle. Aineisto koostui 202 varmistetusta MS-potilaasta ja tutkimusta koskevat tiedot kerättiin retrospektiivisesti potilasasiakirjoista. Naisten ja miesten suhde oli 2.7 ja ikävakioitu insidenssi 10.3 CI 95%: 8.8-11.7).

Insidenssikohortin Coxin regressioanalyysissä primaarisprogressiivinen taudinkulku (PPMS) (p=0,040), multippelit (p=0,011), motoriset (p=0,000), sensoriset (p=0,037) sekä visuaaliset (p=0,008) ensioireet, pitkittynyt viive diagnoosiin (p=0,000) sekä potilaan korkea ikä diagnoosihetkellä (p=0,005) ennustivat edenneempää tautia. Erillisessä relapsoivaa-remittoivaa taudinkulkua (RRMS) sairastavien potilaiden analyysissä multippelit (p=0,013) ja motoriset (p=0,005) ensioireet, aktiivinen tupakointi (p=0,047), pitkittynyt viive diagnoosiin (p=0,000) sekä potilaan korkea ikä diagnoosihetkellä (p=0,003) ennustivat edenneempää tautia. Ne tupakoitsijat, joilla oli lisäksi muita samanaikaisia sairauksia (depressio ja/tai diabetes) olivat suurentuneessa riskissä saavuttaa EDSS 2.5 seurannan loppuun mennessä ja multivariaabelissa Coxin regressioanalyysissä aktiivisten tupakoitsijoiden riski saavuttaa EDSS 2.5 oli yli kaksinkertainen verrattuna tupakoimattomiin. Kun aggressiiviset RRMS-tapaukset suljettiin pois Kaplan-Meyerin analyysista, havaittiin, että RRMS-potilaat, joilla oli käytössä taudinkulkua muokkaava lääkitys, saavuttivat seurannan loppuun mennessä EDSS 2.5 –tason myöhemmin kuin ne, joilla ei ollut lääkitystä (log rank p=0,006). Tutkimuksessa havaittiin, että toimintakyvyn heikentymistä voidaan havaita jo lyhyessä seurannassa, mutta yhä tarvitaan kuitenkin pidemmän seuranta-ajan tutkimuksia, jotta voitaisiin tutkia myös pitkäaikaisennusteeseen vaikuttavia tekijöitä.

1 VOCABULARY

AMS	Aggressive multiple sclerosis
ASC	Adult stem cells
BBB	Blood-brain barrier
BMS	Benign multiple sclerosis
CIS	Clinically isolated syndrome
CNS	Central nervous system
CSF	Cerebrospinal fluid
DIS	Dissemination in space
DIT	Dissemination in time
DMT	Disease modifying treatment
EDSS	Extended disability status scale
EP	Evoked potential
HSC	Hematopoietic stem cells
IFN	Interferon
IgG	Immunoglobulin G
KM	Kaplan-Meyer
MBP	Myelin basic protein
MRI	Magnetic resonance imaging
MSC	Mesenchymal stem cells
MxA	Myxovirus resistance protein A
NEDA	No evidence of disease activity’
NSC	Neural stem cells
PPMS	Primary progressive multiple sclerosis
S1P	Sphingosine 1-phosphate
SPMS	Secondary progressive multiple sclerosis
STC	Stem cell therapy
RCT	Randomized controlled trial
RIS	Radiologically isolated syndrome
RRMS	Relapsing-remitting multiple sclerosis

2 INTRODUCTION

Multiple sclerosis is a chronic inflammatory and neurodegenerative autoimmune disease of the brain and spinal cord. In Finland MS is the most common disease of the central nervous system (CNS) among young adults and also the most common demyelinating disease (Tienari 2016). Approximately 2.5 million people globally and more than 7000 people in Finland are affected by MS (Dendrou et al. 2015, Tienari 2016). The average age of disease onset is approximately 30 years (Dendrou et al. 2015).

Prognosis is highly individual, but approximately 50% of patients have reached a permanent disability after 25 years from diagnosis (Dendrou et al. 2015). The course of multiple sclerosis can be divided into two main types: Relapsing-remitting multiple sclerosis (RRMS) and primary progressive multiple sclerosis (PPMS) (Lublin et al. 2014). In a previous Finnish study, 89% of patients the disease began as RRMS, characterized by recurring relapses and remission phases, but about 11% of patients were affected by PPMS, which leads to more steady disability accumulation (Sumelahti et al. 2014). Like said, the degree of progression in MS varies, but approximately after seven years from RRMS initiation a secondary phase begins and disease reaches the secondary progressive (SPMS) phase, characterized by accumulating disability and paucity of exacerbations (Grigoriadis and van Pesch 2015).

Comorbidity denotes the presence of additional diseases co-occurring with MS. Comorbidity in MS has been linked to increased delay of diagnosis, more frequent hospitalizations, lower quality of life, faster progression of the disease and higher mortality (Capkun et al 2015, Marrie et al. 2009, 2015a, b). Most common comorbidities include depression, anxiety, hypertension, hyperlipidemia and chronic lung disease (Marrie et al. 2015c). Smoking and obesity in childhood and adolescence have been proven to be risk factors for MS (Gianfrancesco et al. 2014, Hawkes 2007, Hedström et al. 2013, Hernan et al. 2005, Langer-Gould et al. 2013, Munger et al. 2013, Ramanujam et al. 2015, Riise et al. 2003).

The first line disease-modifying treatments (DMT) developed for MS are effective mainly in the RRMS (Palmer 2013). Treatment aims at reduction of symptoms and disability accrual, which lead to better quality of life and today also prevention of the disease progression (Palmer 2013). Current first line choises of medication include older injectables,such as interferon beta (IFN-β) and glatiramer acetate and newer peroral medications, dimethyl fumarate and teriflunomide (Multiple sclerosis: Current care guidelines 2015). Other treatment choices include peroral fingolimod and infusion treatments, such as mitoxantrone, alemtuzumab, natalizumab and daclizumab (Multiple sclerosis: Current care guidelines 2015). Treatment option in PPMS is ocrelizumab, which was recently approved for both RRMS and PPMS by the U.S. Food and Drug Administration (FDA) (Hauser et al. 2015, Montalban et al. 2015).

3 EPIDEMIOLOGY

Multiple sclerosis is distributed geographically unevenly and predominantly affects northern Europeans (Sumelahti et al. 2001). The prevalence of multiple sclerosis is highest in Scandinavia and is higher than average for example in North-America, United Kingdom and Ireland populated by the ancestors of the scandinavians (Simpson et al. 2011). The MS prevalence is globally around $120/10^5$ personyears and incidence around $7/10^5$ personyears (Compston and Coles 2002).

Finland is a high risk district and prevalence is about $130/10^5$ personyears and yearly incidence about $7/10^5$ personyears (Multiple sclerosis: Current care guidelines 2015). MS is more common in the western than in the southern Finland, even if the Finnish population is regarded genetically homogenous (Sumelahti et al. 2001, 2014). Prevalence as high as $200\text{-}300/10^5$ has been reported in the south-western area of Seinäjoki (Sumelahti et al. 2001).

This is at least in part caused by familial clustering (Sumelahti et al. 2001). At the same time the rapidly increased incidence indicates action of yet unidentified environmental factors (Sumelahti et al. 2001).

MS incidence is influenced by genes and environmental factors, such as latitude, sex and ethnicity (Pugliatti et al. 2006). According to Danish multiple sclerosis registry studies MS incidence decreased through the 1950s, then increased among the male population and since 1970s increased substantially among the female population (Koch-Henriksen et al. 2011). At the same time the female to male ratio has increased from 1950 to 1999 from 1.3:1 to 2.2:1 (Koch-Henriksen et al. 2011). The increased prevalence is due to rising incidence, but also due to better survival of MS patients seen in the markedly increased number of old MS patients (Koch-Henriksen et al. 1999).

4 CAUSES OF MULTIPLE SCLEROSIS

The exact cause of MS remains unknown, but several environmental as well as genetic factors have been identified as aetiologic factors of MS.

It seems that multiple sclerosis manifests in genetically susceptible patients under the influence of environmental factors (Compston and Coles 2002). The concordance of monozygotic twins was 24% in the Danish studies and for dizygotic twins it was 3%, like for any other siblings (Koch-Henriksen et al. 2011). The risk is 7-10 times higher in the children and siblings of a multiple sclerosis patient (Koch-Henriksen et al. 2011). Epigenetic and post-genomic events have effect in the development of MS (Grigoriadis and van Pesch 2015). Multiple sclerosis seems to be polygenic and multiple polymorphisms contribute to disease development and thus about 30% of the disease risk can be explained with genetic factors (Dendrou et al. 2015). The strongest susceptibility gene is HLA-DRB1*15, which elevates the

odds ratio for homozygotes to 7.0 and for heterozygotes to 3.5-5.0 (Pugliatti et al. 2006). Other genes in the human leukocyte antigen gene cluster, such as HLA-A and HLA-B and over 100 non-HLA-regions have been linked to multiple sclerosis susceptibility, but have milder effect on the susceptibility of MS (Pugliatti et al. 2006). Odds ratios for the non-HLA-genes range between 1.09-1.34 (Pugliatti et al. 2006). These genomic regions overlap considerably with other autoimmune diseases, but little with other neurodegenerative diseases, which reinforces the autoimmune theory of MS (Dendrou et al. 2015).

Environmental factors have been studied extensively, but no single prominent factor has yet been discovered. Low exposure to ultraviolet radiation and vitamin D deficiency, smoking, shift work, obesity and Epstein-Barr virus infection and upper respiratory infections have been associated with increased risk of MS. Physical trauma, emotional stress or vaccinations have not been linked to risk for multiple sclerosis. (Grigoriadis and van Pesch 2015, Mowry 2011)

Smoking is one of the strongest risk factors for MS (Hawkes 2007, Hedström et al. 2013, Hernan et al. 2005, Riise et al. 2003). Cumulative dose, duration and intensity of smoking influence the risk regardles of age at smoking debut (Riise et al. 2003). The risk is reduced to the level of non-smokers in a decade after cessation of smoking (Riise et al. 2003). Smoking also accelerates disease progression (Healy et al. 2009). In a cross-sectional survey and longitudinal follow-up by Healy et al. (2009) 1465 patients with clinically definite MS were followed approximately three years. It was found that smokers' disease was significantly more severe, they progressed faster and their T2-weighted lesion volume increased and brain parenchymal fraction decreased faster than those of never-smokers.

Furthermore, the intestinal microbiome and diet with high fat and salt content may alter the immune responses and contribute to the development of MS (Grigoriadis and van Pesch 2015). Obesity is a chronic, inflammatory state (Aguilar-Valles et al. 2015). It seems that the proinflammatory adipokines produced by adipose tissue become dominant in obesity and this imbalance functons as a link between obesity and autoimmune diseases, such as

multiple sclerosis (Aguilar-Valles et al. 2015). The association between obesity in childhood and adolescence and increased risk of MS in females has been established (Gianfrancesco et al. 2014, Langer-Gould et al. 2013, Munger et al. 2013).

5 PATHOGENESIS

5.1 Immunology of relapsing-remitting multiple sclerosis

Immune cell infiltration and focal inflammation is more prominent in RRMS and early in the disease (Grigoriadis and van Pesch 2015). Immune dysregulation involves both innate and adaptive immune systems (Grigoriadis and van Pesch 2015). According to the predominate theory demyelination is caused mainly by autoreactive T- and B-lymphocytes which initiate abnormal responses against autoantigens of the myelin sheath, but also by aberrant function of regulatory cells (Dendrou et al. 2015, Grigoriadis and van Pesch 2015). Microbes and viruses can activate T cells, B cells and monocytes through molecular mimicry (Compston and Coles 2002, Dendrou et al. 2015).

Dendritic cells become activated after recognizing an antigen and present the antigen to the CD4+ T cells and CD8+ T cells (Elovaara and Soilu-Hänninen 2006, Grigoriadis and van Pesch 2015). T cells express adhesion molecules and penetrate the blood brain barrier (BBB) at the choroid plexus (Compston and Coles 2002, Dendrou et al. 2015, Grigoriadis and van Pesch 2015). After infiltrating to the CNS they are reactivated by microglia and dendritic cells resulting in differentation to IFN-γ secreting Th1 and IL-17 secreting Th17 cells (Dendrou et al. 2015). Th17 cells also produce matrix metalloproteinase and reactive oxygen species which increase the permeability of BBB (Grigoriadis and van Pesch 2015). T cells release inflammatory mediators which cause breakdown of BBB and injury of axons and glia causing

loss of myelin sheath and oligodendrocytes (Compston and Coles 2002, Dendrou et al. 2015). Number of CD8+ T cells correlates with the extent of axonal damage (Dendrou et al. 2015).

Activated microglia produce pro-inflammatory cytokines and chemokines, which attract macrophages from the periphery (Elovaara and Soilu-Hänninen 2006). They produce toxic inflammatory mediators and reactive oxygen and nitroges species resulting in oxidative injury of axons and mitochondrial dysfunction (Grigoriadis and van Pesch 2015). This causes demyelination and axonal loss (Grigoriadis and van Pesch 2015). Microglia and macrophages remain activated throughout the disease (Dendrou et al. 2015).

Microglia and astrocytes produce neurotrophic growth factors and microglia also clear cell debris, which makes them essential for remyelination, but over time this leads to gliosis creating a physical barrier to remyelination (Compston and Coles 2002). This results in brain atrophy, which is related to permanent disability accumulation (Compston and Coles 2002). Astrocytes control infiltration of leukocytes to the CNS and regulate the activity of microglia, oligodendrocytes and adaptive immune cells (Grigoriadis and van Pesch 2015).
Antigens also activate the B cells which penetrate the CNS and produce antibodies intrathecally (Elovaara and Soilu-Hänninen 2006, Grigoriadis and van Pesch 2015). Immunoglobulin G (IgG) antibodies activate the complement resulting in membrane attack complex formation and demyelination (Elovaara and Soilu-Hänninen 2006).

Decreased amount and abnormal function of regulatory T cells may cause the appearance of the autoreactive T and B cells. These cell types may also be resistant to suppressive actions of regulatory T-cells. (Dendrou et al. 2015)

5.2 Immunology of progressive multiple sclerosis

In PPMS there are less inflammatory lesions, which are also smaller (Confavreux and Vukusic 2006). Cortical demyelination and diffuse axonal injury throuhgout the normal-appearing white matter are more pronounced in progressive forms of MS (Grigoriadis and van Pesch 2015). Axonal loss is most prominent in the secondary progressive phase. (Compston and Coles 2002) Degeneration is characterized by axonal loss, gliosis and astrocyte proliferation (Elovaara and Soilu-Hänninen 2006).

Progression is caused by axonal damage triggered by inflammation but it seems to proceed independent of that. Progression may start early, even before the first clinical signs of multiple sclerosis. (Compston and Coles 2002)

The number of B cells increases with age in primary or secondary progressive diseases (Dendrou et al. 2015). CNS infiltrating lymphocytes may cause the formation of tertiary lymphoid structures into the meninges of patients with progressive disease form (Elovaara and Soilu-Hänninen 2006). These formations may be responsible of maintaining the B cell responses in the CNS, but their significange in MS pathogenesis is still unclear (Elovaara and Soilu-Hänninen 2006). Microglia are activated throughout the normal appearing white matter and in the inflammatory plaques (Elovaara and Soilu-Hänninen 2006). They produce reactive oxygen and nitrogen species which cause demyelination of the normal appearing white matter, but also in the gray matter resulting in neuroaxonal damage and brain atrophy (Elovaara and Soilu-Hänninen 2006).

5.3 Signs of blood brain barrier damage

Blood brain barrier (BBB) damage in MS pathogenesis is observed in cerebrospinal fluid (CSF) finding typical of BBB damage is increased protein level and in the case of MS increased intrathecal IgG synthesis which can be seen in electrophoresis as oligoclonal bands and as elevated IgG index. The IgG index is the ratio of CSF IgG to CSF albumin to the ratio of serum

IgG to serum albumin. IgG index of over 0.7 indicates intrathecal IgG synthesis. (Rammohan 2009)

BBB breaching can be observed with magnetic resonance imaging (MRI) as gadolinium-enhancing lesions indicating acute inflammation (Mowry 2011). Lesions have a predilection for the periventricular, juxtacortical, infratentorial and brain stem white matter and depending on the cite of the lesion, demyelination can cause variable symptoms that cause a clinical exarberation called bout (Multiple sclerosis: Current care guidelines 2015).

6 DIAGNOSIS

6.1 Basis of the diagnosis

Currently MS is diagnosed using the McDonald criteria 2010. The diagnosis is a clinical outcome of clinical and paraclinical tests. Paraclinical tests used in the diagnosis of MS are MRI, evoked potentials (EP) and CSF studies including protein content, IgG index and electrophoresis. (Multiple sclerosis: Current care guidelines 2015)

6.2 Diagnosis of RRMS

Diagnosis of RRMS requires exclusion of other possible causes of symptoms and evidence of dissemination in time (DIT) and space (DIS). Therefore McDonald criteria 2010 are fulfilled when patient has suffered from at least two clinical relapses and lesions of at least two functional systems are present. In this case no additional tests are needed.

If patient has had at least two clinical relapses, but has only one objective clinical CNS lesion, dissemination in space needs to be shown with MRI or as a new relapse caused by lesions of another functional system. MRI dissemination in space requires at least two T2 lesions in at least two of the following cites of CNS: Periventricular, juxtacortical or infratentorial white matter or medulla. (Multiple sclerosis: Current care guidelines 2015)

If a patient has has only one clinical relapse, but has at least two clinical CNS lesions, dissemination in time needs to be demostrated by additional clinical relapse or by MRI. MRI dissemination in time requires gadolinium-enhancing and non-enhancing lesions in a single MRI or at least one new T2 or Gd-enhancing lesion in a single MRI. If patient has had only one clinical relapse and one CNS lesion (CIS patient), dissemination in space and time needs to be shown in a previously described manner. (Multiple sclerosis: Current care guidelines 2015)

6.3 Diagnosis of PPMS

PPMS can be diagnosed when patient has had at least one year of steady progression and at least two of the following criteria are fulfilled:

1. Dissemination in space based on one or more T2 lesions in regions characteristic of MS (periventricular, juxtacortical or infratentorial white matter)
2. Dissemination in space based on at least two T2 lesions of brain stem
3. Positive CSF studies (oligoclonal bands, isoelectric focusing or elevated IgG index)

(Multiple sclerosis: Current care guidelines 2015)

7 DISEASE COURSE

7.1 Disease course in Finnish MS population

In a previous Finnish study 89% of patients were affected by RRMS and 11% by PPMS (Sumelahti et al. 2014). Multiple sclerosis can be considered as a single disease with different patterns of evolution (Confavreux and Vukusic 2006). Relapsing-remitting course of the disease can be regarded as pre-progression phase before converting to secondary progressive disease (SPMS) (Confavreux and Vukusic 2006). PPMS and SPMS have similar onset age and initial symptoms at onset of progressive phase, but accumulation of disability is faster and occurs earlier in primary progressive MS (Confavreux and Vukusic 2006). RRMS is more common in women (female/male ratio 2.2 for RRMS and 1.3 for PPMS) and begins earlier than PPMS (Sumelahti et al. 2014). For example in a Finnish 30-year follow-up study the mean age at diagnosis was 36.3 in RRMS group and 45.3 years in PPMS group (Sumelahti et al. 2014).

7.1 CIS

RRMS is initially presented as the first neurological symptom, referred to as clinically isolated syndrome (CIS) after an asymptomatic period of unknown duration (Kantarchi and Weischenker 2006). CIS is followed by a remission period, but not all patients develop any other symptoms (Kantarchi and Weischenker 2006). Usually relapses occur with highly variable rate, median interval between relapses being approximately one year (Compston and Coles 2002).

Disease-modifying therapy can reduce the risk of developing second demyelinating event, which makes it interesting to search for early prognostic factors of disease progression from CIS to relapsing-remitting phase (Mowry 2011). It has been established that non-white race, younger age and lower number of functional systems involved are associated with higher risk for second attack (Mowry 2009).

7.2 RRMS

Relapsing-remitting phase is characterized by relapses of acute neurological symptoms ending up with partial or complete remission. Relapses are mainly caused by acute inflammation. Symptoms can be new or previous symptoms can worsen. (Confavreux and Vukusic 2006)

Bout is a new or abruptly worsened neurological symptom lasting at least 24 hours and at most 4 weeks. A bout should be separated from worsening of previous symptoms due to temperature or infection. Bouts are treated with high dose i.v. steroids, which shortens the duration of symptoms but does not seem to have effect on the long-term prognosis. (Multiple sclerosis: Current care guidelines 2015)

Symptoms include for example muscle weakness, spasticity, sensory symptoms, optic neuritis, diplopia and cerebellar disturbance including dysarthria, ataxia and tremor. Slowed cognition, impaired memory and depression are common especially in progressive MS. Affected neurons conduct impulses slower and may show mechanical (Lhermitte's symptom) and heat sensitivity (Uhthoff's phenomenon). Demyelinated axons may "cross-talk" causing paroxysmal symptoms, such as trigeminal neuralgia or ataxia. (Compston and Coles 2002)

Plaques can be partially repaired by remyelination at least early in the disease resulting in multifocal sclerotic lesions (Dendou et al. 2015). Remyelination, sodium channel formation and neuronal plasticity compensate the damage causing the acute symptoms to resolve and appear again (Ruutiainen et al. 2006). Accompanying axonal injury causes disability accumulation (Kantarchi and Weinshenker 2005). Approximately 75% of RRMS patients convert to SPMS in 25 years from disease onset (Confavreux and Vukusic 2006). Conversion to secondary progression is believed to occur when threshold of axonal damage is crossed and the neuronal plasticity can no longer compensate (Confavreux and Vukusic 2006). Secondary progressive MS is characterized by CNS atrophy and progressive disability accumulation (Dendou et al. 2015).

7.3 PPMS

PPMS is characterized by absence of relapses and paucity of radiological evidence of acute inflammation from onset. Progressive course is itself a predictor of poor outcome, but also involvement of at least three functional systems in PPMS serves as a predictor of worse outcome. The delay in seeking medical care is often longer in patients with PPMS than in patients with RRMS due to lack of clear exacerbations. (Confavreux and Vukusic 2006)

7.5 RIS

Incidental MRI findings consistent with multiple sclerosis that are not associated with any clinical symptoms of MS are referred to as radiologically isolated syndrome (RIS) and not concidered as a form of multiple sclerosis since it lacks sufficient evidence of excistence of multiple sclerosis. About 30% of RIS patients have an exaberbation in 5 years. (Multiple sclerosis: Current care guidelines 2015)

8 CLASSIFICATION OF DISEASE ACTIVITY

8.1 Active and non-active MS

All types of MS (RRMS, PPMS and CIS) can be further categorized in active and non-active depending on the manifestations of clinical relapses presence of new T2- or gadolinium-

enhancing lesions over a certain period of time in RRMS , or progression of disability in both RRMS and PPMS (Grigoriadis and van Pesch 2015). In addition to disease course, classification in active and non-active forms is important in selecting patients to disease modifying therapies.

8.2 Aggressive and benign MS

The course of multiple sclerosis varies dramatically between individuals. Others develop only minimal disability over the course of the disease but others suffer from aggressive disease with rapid disability accumulation and repeated severe attacks. (Rush et al. 2015)

Multiple sclerosis is considered benign if the disease is minimally progressive and does not cause substancial disability accumulation (Confavreux and Vukusic 2006, Correale et al. 2012). Symptoms of benign multiple sclerosis are mainly motor (Correale et al. 2012). The criteria for benign multiple sclerosis (BMS) are still controversial, but EDSS (Extended Disability Status Scale) below 3 after 10 years from disease onset is widely used as a criterion for BMS (Correale et al. 2012). It seems that BMS patients principally suffer from cognitive disability, fatigue, pain and depression (Correale et al. 2012). It has been found that male gender, lower number of relapses in the first 5 years and baseline cognitive impairment and T1 lesion burden are risk factors for BMS (Correale et al. 2012). BMS incidence has been ranging between 5 and 64 % depending on the criteria used but for example in a Correale et al. (2012) study the incidence was 12.5%.

The terms of aggressive and malignant MS have been ambiguous, but there has been increasing interest in defining the aggressive multiple sclerosis. The term of malignant disease should be reserved to fulminant multiple sclerosis, such as the Marburg variant that results in death within months or few years (Menon et al. 2013, Rush et al. 2015).

Menon et al. (2013) have categorized aggressive multiple sclerosis (AMS) into three groups. AMS1-group reached EDSS 6 within 5 years from onset symptom, AMS2-group reached EDSS 6 by age 40 and AMS3-group converted to SPMS within 3 years from RRMS onset. The researchers constituted a combined population of the patients that did and did not (comparator cohort) fulfill the criterion for each AMS group. 5.5% of the combined AMS1-group were categorized as AMS1, 14.0% of the combined AMS2-group were categorized as AMS2 and 4.0% of the combined AMS3-group were categorized as AMS3. In both AMS1 and AMS2 groups the AMS patients were more likely to be male and have primary progressive disease course compared to control cohort. AMS1 patients were more likely to be older and AMS2 patients younger than the controls at the time of MS onset. AMS3 patients were more likely to be male and older at MS onset than the controls. Therefore, depending on the definition used in approximately 4-14% of patients the disease course could be defined as aggressive. (Menon et al. 2013)

According to Rush et al. (2015) aggressive multiple sclerosis can be defined as any type of MS that is rapidly progressive. RRMS can be defined aggressive when EDSS score reaches 4 within 4 years from onset, annual relapse rate exceeds two relapses per year and resolution from those is imperfect, follow-up MRI shows more than two new or enlarging T2-lesions or gadolinium-enhancing lesions despite treatment or the patient does not respond to treatment with one or more DMT in a year. Male sex, disease onset at older age, cognitive, motor, cerebellar and/or spinchter impairment, especially if multifocal, more severe exacerbations and poor recovery indicate more severe disease course. High lesion load, infratentorial lesions or atrophy at first MRI and presence of new T2 or Gd-enhancing lesions at follow-up MRI may also help to identify aggressive MS. (Rush et al. 2015)

In a study of Kaunzer et al. (2016) the criteria for AMS were

1) two or more relapses in a year after MS onset and two or more Gd-enhancing lesions on brain MRI
2) one relapse if it results in sustained baseline EDSS score of 3 and two or more Gd-enhancing lesions on brain MRI.

In this study 7.4 % of all MS patients had aggressive multiple sclerosis. (Kaunzer et al. 2016)

According to another classification by Gholipour et al. (2011) malignant (or aggressive) MS could be described as disease with rapid disability accrual of EDSS 6 in 5 years after disease onset. In this study the incidence of malignant MS was 12.11%. Malignant disease could be divided to transient and sustained malignant MS. Older, male patients and smokers were more likely to develop sustained malignant MS. (Gholipour et al. 2011)

9 MORTALITY AND FACTORS AFFECTING PROGNOSIS AND SURVIVAL IN MS

Multiple sclerosis is associated with a higher risk of death compared to general population (Multiple sclerosis: Current care guidelines 2015). In over half of the MS patients the death is caused from complications of multiple sclerosis (Phadke 1987, Bronnum-Hansen et al. 2004). Multiple sclerosis shortens life expectancy approximately 10 years, but in patients with onset occurring over the age of 50 the life expectancy is even shorter (Phadke 1987, Bronnum-Hansen et al. 2004). In Finland the mortality rate is 2.2-fold in male and 3.4-fold in women with multiple sclerosis than in age-matched controls (Sumelahti et al. 2010).

The beneficial survival is associated with visual or sensory initial symptoms, while motor, cerebellar or spinchter symptoms and initially progressive course, male gender, older age and multifocal symptoms at onset relate to worse outcome (Eriksson et al. 2003, Gholipour 2011, Kantarchi and Weinshenker 2005).

Smoking after the diagnosis of MS is associated with acceleration of disease progression and cessation of smoking decelerates the progression (Hedström et al. 2013, Ramanujam 2015, Zivadinov et al. 2009). MRI-scans of the smokers show increased number of contrast-

enhancing lesions, increased T1 and T2 lesion volumes and brain atrophy (Zivadinov et al. 2009).

Studies have found that the incidence of infections, cardiovascular diseases, other systemic diseases and psychiatric disorders is higher and incidence of cancer lower in the MS population (Chapkun et al. 2015). In a large population-based study comorbidities were associated with increased mortality but the MS population had less total comorbidity than the matched population (Marrie et al. 2015). Higher mortality was observed only for depression compared to matched controls (Marrie et al. 2015).

Usually the future course of the disease can be predicted quite reliably from the first 5 years in the disease (Confavreux and Vukusic 2006). Recognition of early predictive factors of conversion of CIS to clinically definite MS and RRMS conversion to SPMS is important in selection of patients to disease modifying therapies (Eriksson et al. 2003).

PPMS is associated with worse prognosis and more rapid disability accrual (Kantarchi and Weinshenker 2005, Levic 1999). In RRMS high relapse frequency predicts worse outcome and conversion to secondary progression (Kantarchi and Weinshenker 2005). In relapsing-remitting MS incomplete recovery from relapses and secondary progression together accumulate fixed disability (Compston and Coles 2002). If the first MRI shows signs of MS in a CIS patient, the risk of developing multiple sclerosis is 88% and if not, the risk is 19% (Brex et al. 2002). Increasing MRI lesion load indicates higher risk of developing MS (Confavreux et al. 2000).

Conversion to secondary progression and time to reach EDSS 6 can be predicted from greater number of functional systems involved, high relapse rate, poor remission from early exacerbations and short time to early disability (Eriksson et al. 2003). Patients who reached EDSS 3 faster had a shorter interval between EDSS 3 and EDSS 6 (Eriksson et al. 2003). Early cognitive symptoms also imply higher risk of secondary progression (Eriksson et al. 2003).

None of the early predictors could predict rate of secondary progression indicating that pathogenesis of secondary progression is separate from pathogenesis of early relapsing-remitting phase (Confavreux and Vukusic 2006, Confavreux et al. 2000, Eriksson et al. 2003).

Pregnancy seems to affect the relapse rate. During the pregnancy, relapse rate is at its lowest in the third trimester and rises instantly after parturition. After 3 months the relapse rate lowered to the pre-pregnancy level. (Kantarchi and Weinschenker 2005).

10 TREATMENT

10.1 Effect of disease modifying treatment

Prior to current disease modifying therapies multiple sclerosis was handled with immunosuppressive drugs, such as cyclophosphamide. They were problematic not only because of their toxicity but also for their modest efficacy. (Rush et al. 2015)

Treatments are not specific enough and therefore they often have side-effects including flu-like symptoms, opportunistic infections and other autoimmune and malignant diseases. Injectable treatments often cause adverse skin reactions, such as erythema, itching, edema and occasionally lipoatrophy (Dendrou et al. 2015, Elovaara and Soilu-Hänninen 2006). These side-effexts can weaken log-term adherence to therapy (Confavreux and Vukusic 2006).

Current immunological therapies are targeted mainly against infiltration of CNS by immune cells seen most prominently in relapsing-remitting course of the disease (Kantarchi and

Weinshenker 2005). DMT:s cause reduction of relapse frequency, attack severity and radiological evidence of inflammation (Kantarchi and Weinshenker 2005). Early intervention may prevent disability accumulation caused by axonal loss, but this has not been established yet due to the long time needed for disability accumulation (Confavreux and Vukusic 2006). Therefore DMT:s are currently used in RRMS patients who show continuing active inflammation.

According to current knowledge multiple sclerosis begins with an asymptomatic phase of variable duration. Even the first MRI often shows dissemination in time and/or space proving that the disease has already been proceeding before the initial symptoms. (Elovaara and Soilu-Hänninen 2006)

MRI can be used in evaluation of treatment effectiveness, especially in the first years from treatment onset. New or expanding gadolinium-enhancing or T2-weighted lesions signal disease activity and are a subject for concideration of treatment enhancement. Patient who suffers from disease activity during use of first line medication is often switched to secind line medication, such as natalizumab. (Multiple sclerosis: Current care guidelines 2015)

10.2 Current treatment practice in Finland

The Social Insurance Institution of Finland requires at least two confirmed episodes of neurological dysfunction or one episode and temporally distinct MRI finding of demyelination to grant reimbursements for first-line treatments (http://www.kela.fi/laake303 8.7.2016). Fingolimod (Gilenya®) is reimbursable if the relapsing-remitting MS is very active despite of at least one DMT. Thus the time interval from disease onset to the beginning of disease modifying treatment is lengthy and allows disease development in the early phase (Elovaara and Soilu-Hänninen 2006). On the other hand not every patient needs DMT and it may cause yet unidentified adverse effects in the long run (Elovaara and Soilu-Hänninen 2006).

10.3 Injectable treatments

Injectable IFN beta drugs were the first disease modifying treatments for multiple sclerosis. Betaferon was approved for sale in Finland in 1995, Avonex in 1997, Rebif in 1998 and Extavia in 2008 (http://www.fimea.fi/laakehaut_ja_luettelot/laakehaku 12.7.2016). The mechanism of action is not completely clear, but these drugs are thought to shift the immune response from Th1 to Th2 reducing the occurrence of relapses approximately by 30%, alleviating the symptoms and prolonging the time between the exacerbations (Palmer 2013). Some patients develop neutralizing antibodies against IFN betas, which results in low IFN-induced MxA-levels (Palmer 2013). MxA-levels should be controlled 12 and 24 months after treatment onset and low levels should be controlled after 3-6 months (Palmer 2013). Antibody formation after 24 months is extremely rare (Palmer 2013). IFNs may cause headache, depression, liver enzyme elevation, thrombocytopenia and leukocytopenia (Palmer 2013).

Glatiramer acetate (Copaxone®) received a trade license in Finland in 2004 (http://www.fimea.fi/laakehaut_ja_luettelot/laakehaku 12.7.2016). It is a random polymer of four amino acids found in myelin basic protein (MBP) (Palmer 2013). The mechanism of action is thought to stem from tolerization to MBP and Th1-Th2 shift of immune response (Palmer 2013). Glatiramer acetate reduces the relapses by 32%, but has no effect on the relapse duration or severity (Palmer 2013). Glatiramer acetate can cause adverse cardiovascular effects, such as vasodilatation, tachycardia or difficulty in breathing (Palmer 2013). Antibody formation is more infrequent in patients using glatiramer acetate than patients using interferons and thus laboratory surveillance is not required (Palmer 2013). Neither interferons nor glatiramer acetate seem to have effect on the long-term disability accumulation, but both reduce the amount of MRI lesions and delay conversion of CIS to RRMS (Palmer 2013).

10.4 Peroral treatments

The first peroral treatment to receive a trade license in Finland was fingolimod (Gilenya®) (2011), the second was teriflumode (Aubagio®) (2013) and the third was dimethyfumarate (Tecfidera®) (2014) (http://www.fimea.fi/laakehaut_ja_luettelot/laakehaku 12.7.2016). Aubagio and Tecfidera belong to first-line treatments, but Gilenya is a second-line treatment (Multiple sclerosis: Current care guidelines 2015).

Fingolimod is a sphingosine 1-phosphate (S1P) receptor modulator. Fingolimod mimicks S1P, binding to S1P receptor and causing their internalization. In the absence of S1P receptors lymphocytes fail to exit the lymph nodes reducing the amount of CNS penetrating lymphocytes. Fingolimod reduces the relapse rate significantly more than IFNs or glatiramer acetate (54%). It also reduces MRI lesions by 67%. Fingolimod has effect on atrioventricular conduction and may cause bradycardia and heart block. (Palmer 2013)

Teriflunomide inhibits the mitochondrial enzyme dihydro-orotate dehydrogenase (DHODH) reducing the pyrimidine neogenesis and thus also production of activated T cells. Teriflunomide reduces the relapse rate by 31%, its effect being comparable to IFNs and glatiramer acetate. It also reduces the amount of MRI lesions. Teriflunomide can cause for example influenza, paraesthesia, alopecia, liver enzyme elevation and gastrointestinal side effects. (Palmer 2013)

Therapeutic effects of dimethyl fumarate are due to activation of Nrf2 pathway (nuclear factor like-2), which activates anti-oxidant pathways and is neuroprotective and anti-inflammatory (Palmer 2013). It also shifts the immune response from Th2 to Th1 (Palmer 2013). It reduces relapses by 44-53% and new gadolinium-enhancing lesion formation by 49-89% (Palmer 2013). It can also inhibit disability progression (Palmer 2013). Dimethyl fumatare can cause flushing and gastrointestinal effects, lymphopenia, liver enzyme elevation and acute kidney injury (Elovaara et al. 2008).

10.5 Infusion treatments

Mitoxnatrone (Novantrone®) has been on market in Finland since 1993, first as a treatment for cancer and since 1999 (28) for aggressive relapsing-remitting multiple sclerosis. Natalizumab (Tysabri®) was approved for sale in 2006 and alemtuzumab (Lemtrada®) in 2013. Daclizumab (Zinbryta®) was approved for sale in 2016. (http://www.fimea.fi/laakehaut_ja_luettelot/laakehaku 12.7.2016)

Both mitoxantrone and natalizumab reduce relapses by 66-67% and reduce MRI lesions by 90%, but also retard disability progression in progressive forms of MS (Palmer 2013). Mitoxantrone is a humanized monoclonal antibody, which binds to DNA and RNA and exerts its cytotoxic effects on proliferative and nonproliferative cells (Palmer 2013). It inhibits the proliferation of T cells, B cells and macrophages, disrupts antigen presentation and reduces INF-gamma, TNFα and IL-2 secretion (Palmer 2013). Mitoxantrone increases the risk of infertility, leukaemia and cardiotoxicity (Palmer 2013). Mitoxantrone is administered as infusion every 3 months (Elovaara et al. 2008). Maximum cumulative dose for mitoxantrone is 120 mg, but usually 1-3 teatments are sufficient to alleviate the symptoms (Elovaara et al. 2008, Multiple sclerosis: Current care guidelines 2015).

Natalizumab binds to integrin α4β1 inhibiting interaction between it and vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells, which inhibits the transmigration of mononuclear leukocytes into the CNS. Natalizumab thus also permits opportunistic pathogen ingress into the CNS. JC-virus can cause progressive multifocal leukoencephalopathy (PML), which may cause death or severe invalidity due to progressive white matter damage. Therefore berofe the first natalizumab-infusion the anti-JC-virus antibodies must be tested negative. Anti-JC virus antibodies, prior immunosuppression and increasing duration of natalizumab treatment increase the risk of PML. Natalizumab can also elevate liver enzymes and change blood cell levels, cause infusion reactions, such as

dizzyness, nausea, urticaria and rigidity and increase the risk of other infections, such as urinary tract infection or upper respiratory tract infections. Small amount of patients (6%) may develop neutralizing antibodies against natalizumab, which are tested 6 months after treatment onset. (Palmer 2013)

Alemtuzumab is a humanized monoclonal antibody for CD52, a surface glycoprotein of T cells, B cells, monocytes and macrophages. Binding causes complement and antibody-dependent cytotoxicity resulting in depletion of CD52 expressing cells. B cells recover rapidly, but CD4+ T cells take years to recover. Alemtuzumab elevates the levels of regulatory T cells and decreases the levels of memory T and B cells. Alemtuzumab decreases relapses by 49-55% and also the MRI findings are reduced and the disability accumulation is delayed. Alemtuzumab may increase the risk of developing other autoimmune diseases. (Palmer 2013)

Daclizumab is monoclonal antibody for CD25, IL-2 receptor of the lymphocytes. Thus daclizumab prevents IL-2 dependent activation of lymphocytes. The phase II studies have so far shown 54-80,7% reduction in relapse rates and 70-78% reduction in MRI lesions in patients using different doses and formulations of daclizumab. Daclizumab can cause upper respiratory tract infections and pharyngitis, liver enzyme elevation and cutaneous effects, such as erythema and induration. (Palavra 2015)

10.6 Emerging treatments

10.6.1 Monoclonal antibodies

New monoclonal antibodies (mAbs) are currently under investigation for treatment of multiple sclerosis. Ocrelizumab targets CD20 causing depletion of B cells (Palavra 2015). In the phase II studies ocrelizumab has reduced the relapse rates by 73-80% and amount of

new gadolinium-enhancing lesions on MRI scans by 89-99,8% (Palavra 2015). Ocrelizumab can cause infusion-related reactions, but no unexpected safety issues have emerged (Palavra 2015). Phase III studies are currently ongoing for daclizumab and ocrelizumab and several mAbs are studied at the moment (Palavra 2015). mAbs are evidently effective in the treatment of RRMS, and at least alemtuzumab and natalizumab have been shown to reduce the disability accumulation and partially reverse disability (Palmer 2013).

10.6.2 Stem cell therapies

Stem cell therapies (SCTs) are currently under investigation for treatment of multiple sclerosis. Pluripotent stem cells have a capacity of cell replacement and neuroprotection. Adult stem cells (ASC) including hematopoietic stem cells (HSC), mesenchymal stem cells (MSC) and neural stem cells (NSC) as well as embryonic stem cells can be utilized, but the latter seem to be more prone to teratoma formation. MSCs and HSCs are usually derived from bone marrow and are capable of self-replication making the availability of HSCs and MSCs better than that of NSCs. Nevertheless only NSCs have the ability of remyelination and therefore additional study is needed especially regarding NSCs. (Meamar 2016)

MSCs can be cultured in vitro and administered intrathecally. MSCs secrete several autocrine and paracrine factors that have neurotrophic and neuroprotective actions. Animal models have shown that MSC transplantation can suppress the CNS inflammation and reduce the clinical severity of the disease. (Meamar 2016)

HSC transplantation aims at replacement of the immune system rather than neuroregeneration and thus re-establishment of tolerance to self-proteins. HSCs can be aspirated directly from the bone marrow or mobilized using intravenous chemotherapy or hematopoietic growth factors and collected by leukophoresis. (Meamar 2016).

NSCs are self-replicating multipotent progenitors of developing and adult CNS, which could provide a source of remyelinating cells. NSCs have neurotrophic, immunomodularory and neuroprotective properties. NSC transplantation has been shown to improve EDSS score and reduce the MRI lesions. The results of preclinical studies have been somewhat controversial, and no clinical trials regarding the NSC treatment are currently ongoing. (Meamar 2016).

10.6.3 Laquinimod

Laquinimod is an orally effective carboxamide derivative, taken once a day. Laquinimod has an ability to cross the bloob brain barrier and has multiple effects in and out of CNS. Laquinimod inhibits the entry of leukocytes into the CNS, reduces the infiltration of CD4+ T cells, CD8+ T cells and macrophages, suppresses the Th17 proinflammatory responses, increases the amount of regulatory T cells and modulates the cytokine balance towards an anti-inflammatory milieu. Laquinimod has also effects on B-cell mediated activation of T cells and NF-κB pathways. Laquinimod has also neuroprotective properties resulting in decreased axonal damage, demyelination and oligodendrocyte apoptosis. (Thöne and Linker 2016)

Laquinimod reduces modestly the amount of MRI lesions. Studies using low doses (0,3 mg/day) found no significant effect on clinical exacerbations, EDSS or MSFC (Multiple Sclerosis Functional Composite). Doses of 0,6mg/day have been shown effective in reducing the annual relapse rates and risk of confirmed disability progression, but the information is somewhat conflicting. Lower rates of brain atrophy have also been observed.
Studies on patients with relapsing-remitting and progressive multiple sclerosis and Huntington´s disease are currently ongoing. Laquinimod may answer to the unmet need of therapies for progressive disease forms. (Thöne and Linker 2016)

10.7 Treatment goals

The treatment goals in MS have been amelioration of disease symptoms, to improve the quality of life and reduce the disability accumulation. Today potent and multiple disease modifying therapies have shifted the treatment goals towards the prevention by reducing the disease activity. In clinical trials first goals were reduction of annual relpse rate and attenuation of disease progression, however due to weak correlation with disease activity, MRI correlates were soon introduced as outcomes. New T2 lesions or gadolinium enhancing lesions were followed by new surrogates such as brain atrophy. (Bevan et al. 2014, Fred 2005, Whitaker et al. 1995)

The term 'no evidence of disease activity' (NEDA) is a composite outcome measure for features such as no new or enhancing T2-weighed lesions, no new Gd enhancing lesions, no relapses and no confirmed worsening of Expanded Disability Status Scale scores. Brain volume loss have stronger correlation with disability and it has been suggested that they should be incorporated into NEDA. Unfortunately to date no therapy for MS has achieved a NEDA of geater than 50% and it appears that there will always be MS patients who worsen over time. (Bevan et al. 2014)

Aggressive MS requires therapy that eliminates disease-causing cells and therefore the first-line and most second-line treatments are often ineffective (Rush et al. 2015). If the disease follows an aggressive course from the onset, according to the Finnish Current Care Guidelines second or third line treatments, alemtuzumab, natalizumab or fingolimod should be used (Multiple sclerosis: Current care guidelines 2015). Mitoxantrone can be used if the disease is resistant to these therapies (Multiple sclerosis: Current care guidelines 2015). Nevertheless only alemtuzumab and mitoxantrone deplete the disease-causing cells (Rush et al. 2015). These drugs can cause severe adverse effects, but the risks and benefits should be weighed individually (Rush et al. 2015). When other therapies have failed, stem cell transplantation might be appropriate (Rush et al. 2015). There are other drugs, such as cladribine, cyclophosphamide and rituximab, that deplete disease-causing cells, but those are not currently used in the management of aggressive MS (Rush et al. 2015).

10.8 Window of treatment opportunity

It is postulated that factors early in the disease predict the later outcome and thus it is crucial to identify patients with aggressive disease early. The period of most intense inflammation occurring from the onset symptoms to probably some time before the conversion to secondary progression is the best opportunity for treatment with current DMTs. In aggressive MS this window of treatment opportunity is brief and can close suddenly due to rapid progression of the disease. The goal of treatment is to decelerate the speed of disability accrual and thus prevent the accumulation of permanent disability. Apart from clinically aggressive RRMS, for which induction treatment should certainly be regarded as the first line of treatment, there is a lack of biomarkers to guide early and safe choices between strategies at an individual level. (Edan and Le Page 2013)

Classification of aggressive multiple sclerosis could be used in identification of patients who would need more aggressive treatments, as once a clinical threshold of irreversible disability is reached, the progression of disability is amnesic of the prior activity and clinical history of the disease (Leray et al. 2010). Beyond EDSS 6 the risk-benefit ratio might be unfavourable (Rush et al. 2015).

In a study of Kaunzer et al. (2016) 43 patients with aggressive onset multiple sclerosis (AOMS) were selected for follow-up. Only two patients out of 35 who received first-line medications had NEDA and 22 of them were switched on more aggressive treatments. 7 out of 8 patients who were initially started on aggressive therapies had NEDA. This indicates the need of early optimal treatment for patients suffering from aggressive MS. If the patients showed no change in baseline neurological exam, no relapses and no new or enlarging T2 lesions or gadolinium-enhancing lesions on the MRI scan, they were classified as NEDA. (Kaunzer et al. 2016)

11 MATERIALS AND METHODS

11.1 Case ascertainment

Patients with multiple sclerosis in the health care district of Tampere University Hospital district at Pirkanmaa were recruited in the study from the hospital administrative data registry. The study cohort was selected among 478 cases who had received multiple sclerosis (ICD-10 G35), morbus demyelinans (ICD-10 G37) or retrobulbar or optic neuritis (ICD-10 H46) diagnosis between January 2010 and December 2014. Most of them were initially diagnosed before 1 January 2010 or outside the Pirkanmaa district and some of them did not eventually have multiple sclerosis. Therefore 276 cases were excluded and 202 cases that filled the McDonald diagnostic criteria for definite diagnosis were included in the study. Disease course was classified into RRMS, PPMS and CIS based on criteria by Lublin and Reingold (2014). In Finland, all MS patients are diagnosed by a neurologist according to the McDonald diagnostic criteria (2010). Kurzke Extended Disability Status Scale (EDSS) is used in determination of disability (Kantarchi and Weinschenker 2005).

Patient records of the confirmed MS patients were carefully scrutinized. We collected results on diagnostic MRI, CSF and EP studies. CSF and MRI are routine studies in diagnostics of MS in Finland. Information was collected on the date and quality of the first symptom, the number of possible relapses prior to diagnosis, time lag between initial symptoms and diagnosis~~,~~ disease modifying therapy, comorbidities, pregnancies and smoking. We recorded available MRI dates and findings, including inflammatory activity, new lesion formation and atrophy for the first as well as for the following MRIs. Expanded Disability Status Score (EDSS) was collected at any medication start timepoint and at the end of follow up in 15 June 2016. In case of loss of follow-up, the last EDDS value closes to the follow-up date was used as the final EDSS value. A detailed description on three cases with natalizumab treatment in active MS at onset is included.

11.2 Method

We calculated the crude and age-adjusted incidences for all cases as well as by gender with 95% confidence intervals per 10^5 person years from 1 January 2010 to 31 December 2014. Kaplan Meyer (KM) analysis was employed to study survival and significance was given using log lank test. Survival was assessed from disease onset year and year of birth up to the end of follow up in 15 June 2016. In the survival analyses EDSS 2.5 was used as an endpoint. The hazard ratios (HR) with 95% confidence interval (95% CI) in Cox's univariable and multivariable regression analyses are given.

Categorization for first symptoms resulted in five groups: Visual, sensory, motor, brainstem or multiple/other. The study population was categorized by smoking status into active, past and non-smokers. Distribution of cases by medication, EDSS at medication start in ten-year age groups, final EDSS and EDSS change during the five-year follow-up were studied.

12 Results

12.1 Demographics of the study population

From 1 January 2010 to 31 December 2014 altogether 202 MS cases fulfilled the inclusion criteria of definite MS by the McDonald diagnostic criteria (2010). 18 cases (8.9%) were lost to follow up and 11 (5.4%) due to migration. None of the patients died during the follow-up period and the follow-up information up to 15 June 2016 was complete. The population of Pirkanmaa was 524 447 in the end of 2014. The age-structure remained the same during the 5-year follow-up period (Figure 1).

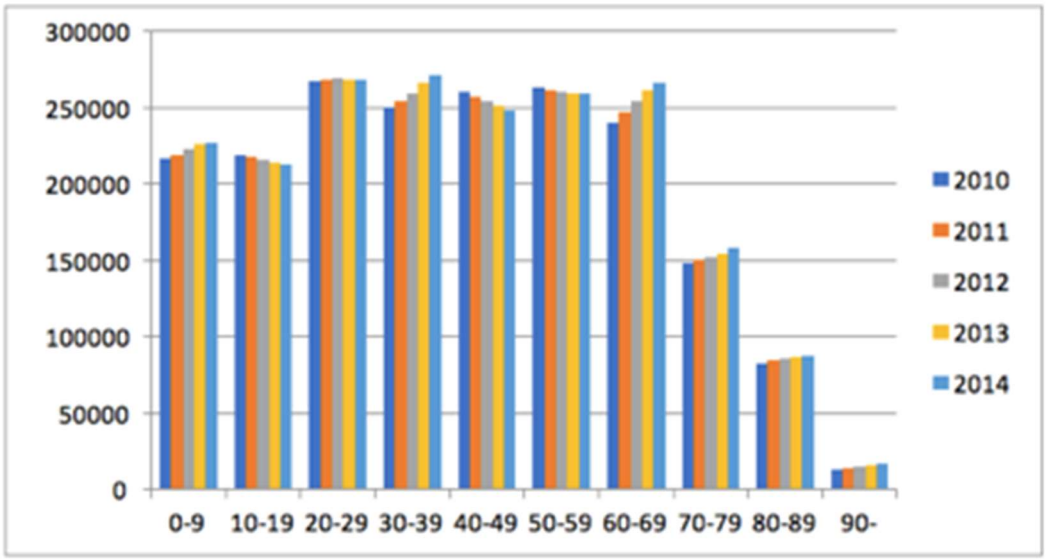

Figure 1. Age-structure during the follow-up period 1 January 2010 to 31 December 2014.

Characteristics of the patients are shown in Table 1. 72.8% (n=147) of cases were female and 27.2% (n=55) were male, the female/male-ratio being 2.7. 92.6% (n=188) of all MS cases were RRMS and 7.4% (n=14) were PPMS. Most frequent onset symptoms originated from visual tract (33.7%, n=68), sensory tracts (32.7%, n=66), and brainstem (16.3%, n=33). Median age at onset symptom was 31 years and at diagnosis 35 years. Most RRMS patients had had one (34.7%) or two (49.4%) attacks before diagnosis. The median diagnostic delay was 1.0 years.

Table 1: Characteristics of cases.

	N	%
Number of cases		
Total	202	
Female	147	72.8%
Male	55	27.2%
F/M-ratio	2.7	
Disease course		
CIS	12	5.9%
MS	190	94.1%
RRMS	176	92.6%
PPMS	14	7.4%
Age at onset		
Median	31	
Mean	32	
Age at diagnosis		
Median	35	
Mean	36	
Diagnostic delay, years		
Median	1.0	
Mean	4.1	
SD	5.9	
First symptom by anatomic level		
Visual tract	68	33.7%
Sensory	66	32.7%
Brainstem	33	16.3%
Motor	19	9.4%
Multiple	14	6.9%
Other	2	1.0%
Comorbidities		
Obesity	32	15.8%
Metabolic	29	14.4%

12.2 Case ascertainment and assessment of MRI

McDonald 2010 criteria were applied. MRI was performed at least once in all cases and CSF studies in 96,0% of cases. EP studies were used in only 5.9% of cases and 58.3% of EP studies were positive. The IgG-index was abnormal in 87.7% of RRMS cases and 84.6% of PPMS cases. The first MRI was indicative of MS in 93.0% of all cases. Activity in first MRI was recorded in 42.0% of RRMS cases and in 7.1% of PPMS cases. Brain atrophy was observed in the first or follow-up MRIs in 46.2% of PPMS cases and in 13.3% of RRMS cases.

12.3 Use of disease modifying treatment

During the follow-up 73.9% (130/176) of RRMS patients started medication with a first line DMT treatment: Avonex® in 22 cases, Betaferon® or Extavia® in 20, Copaxone in 13, Rebif® (22 μg or 44 μg) in 69, Aubagio® in 4 and Tecfidera® in 2. In 53.0% of cases the choice of primary treatment was Rebif®. In four cases treatment was started with natalizumab and in four cases treatment in randomized controlled trial (RCT) remained unknown. 38 RRMS patients did not use any disease modifying treatment.

12.4 Comorbidities and smoking

Active smoking was observed in 24.3% (n=49) of patients during the follow-up period, 14.4% (n=29) of them were past smokers and 43.1% (n=87) did not smoke. In 16.8% (n=37) of cases smoking status was unknown.

Most (n=113, 55.9%) patients were not reported to have any comorbidities. Most commonly patients were obese (n=32, 15.8%) or had one or more metabolic comorbidities (hypertonia, hypercholesterolemia or diabetes mellitus type II) (n=29, 14.4%). Results are shown in Table 1.

12.5 Incidence

From January 1 2010 to December 31 2014 the crude incidence was 7.8 (95% CI: 6.7-8.9) for all cases, 4.3 (95% CI: 3.2-5.4) for men and 11.2 (95% CI: 9.4-13.0) for women. The total age-adjusted incidence was 10.3 (CI 95%: 8.8-11.7), 6.5 (95% CI: 4.8-8.2) for men and 15.1 (95% CI: 12.7-17.5) for women.

Incidence was highest in patients with RRMS in the age group of 30-39 years (19.6, 95% CI: 14.9-24.3) and in PPMS in the age group of 40-49 years (2.1, 95% CI 0.6-3.7). The total incidence for both disease courses and genders was highest in the age group of 30-39 years (21.1, CI 95%: 16.2-26.0). Age specific incidences were higher for women in the age-group of 10-49 years and for men in the age-group of 50-69 years. The highest F/M-ratio was observed in the 10-19 year-age group, in which 9 female and no male patients were observed. The F/M-ratio was 1.0 in the age group of 50-69 years.

12.6 Disability progression in the incidence cohort

Factors associated with a risk of reaching the endpoint of EDSS 2.5 by the end of the follow-up period were analyzed by KM and Cox regression models for the incidence cohort of 202 MS patients from diagnosis.

The mean follow-up time from diagnosis to the end of the follow-up period in 15 June 2016 in the incidence cohort was 5.5 years (5.3-5.7), median was 6.4 years (5.8-6.9). Mean follow-up time in RRMS was 5.7 years (5.4-5.9), median was 6.4 years (5.8-6.9). Mean follow-up time in PPMS was 3.6 years (2.8-4.5) and median was 3.8 years (0.95-6.7).

In KM analysis the risk of progression from timepoint of diagnosis up to the end point of EDSS 2.5 at the end of follow-up for PPMS patients was significantly faster than that for patient with RRMS patients (log rank p=0.00). (Figure 2).

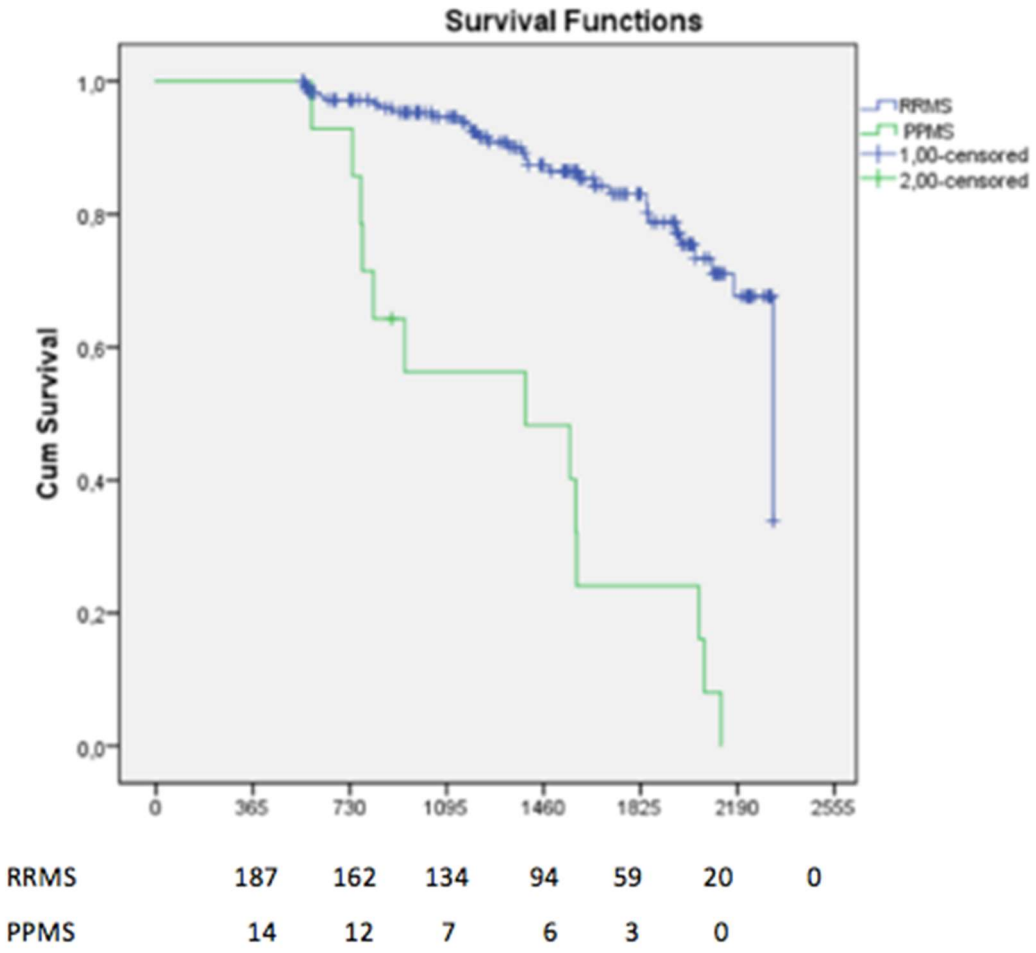

Figure 2. Survival from timepoint of definite MS diagnosis to EDSS change to 2.5 or more for RRMS and PPMS patients diagnosed from 1 January 2010 to 31 December 2014. (log rank p=0.00)

Factors associated with a risk of reaching the endpoint of EDSS 2.5 by the end of the follow-up period in the univariable and multivariable Cox models are shown with HRs and 95% confidence intervals in Table 2. PPMS (p=0.040), longer diagnostic delay (p=0.000) and higher age at first symptoms (p=0.005) in both univariable and multivariable model showed a statistically significant risk. Same was true for visual (p=0.008), sensory (p=0.037), motor (p=0.000) and multiple (p=0.011) first symptoms. In adjusted model no association was found with gender, level of IgG index at diagnosis, first symptoms of brainstem level or number of comorbidities.

Table 2: Cox model. Risk of reaching EDSS 2.5 by the end of follow up in the incidence cohort (n=202).

	UNIVARIABLE			MULTIVARIABLE		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
Disease course						
RRMS	1.0			1.0		
PPMS	7.4	3.8-14.2	0.000	2.7	1.0-6.8	0.040
First symptom						
Visual tract	1.0		0.000	1.0		0.008
Sensory	2.5	1.0-6.1	0.050	3.2	1.1-9.3	0.037
Motor	9.6	3.6-25.6	0.000	10.1	2.8-36	0.000
Brainstem	2.4	0.86-6.6	0.094	2.4	0.63-9.1	0.197
Multiple	3.5	0.89-13.5	0.072	6.8	1.6-23	0.011
Other	4.8	0.58-39.1	0.146	2.5	0.39-2.1	0.425
Gender						
Female	1.0			1.0		
Male	1.6	0.85-2.9	0.147	0.9	0.39-2.1	0.796
Smoking status						
No smoking	1.0		0.165	1.0		0.322
Active smoker	1.8	0.85-3.7	0.125	2.3	0.92-5.7	0.075
Past smoker	0.54	0.16-1.9	0.328	1.0	0.25-3.9	0.992
Smokig status unknown	1.6	0.72-3.4	0.251	1.3	0.55-3.1	0.548
Diagnostic delay	1.1	1.0-1.1	0.001	1.1	1.1-1.2	0.000
Age at initial symptoms	1.1	1.1-1.1	0.000	1.1	1.0-1.1	0.005
IgG index	0.98	0.56-1.7	0.941	1.2	0.66-2.1	0.569
Number of comorbidities	1.0	0.85-1.2	0.777	1.0	0.82-1.3	0.854

Time to end point of EDSS 2.5 at the end of follow-up was shorter among active smokers than that of non-smokers or past smokers in the KM analysis, but the difference was not statistically significant (log rank p=0.121) (Figure 3).

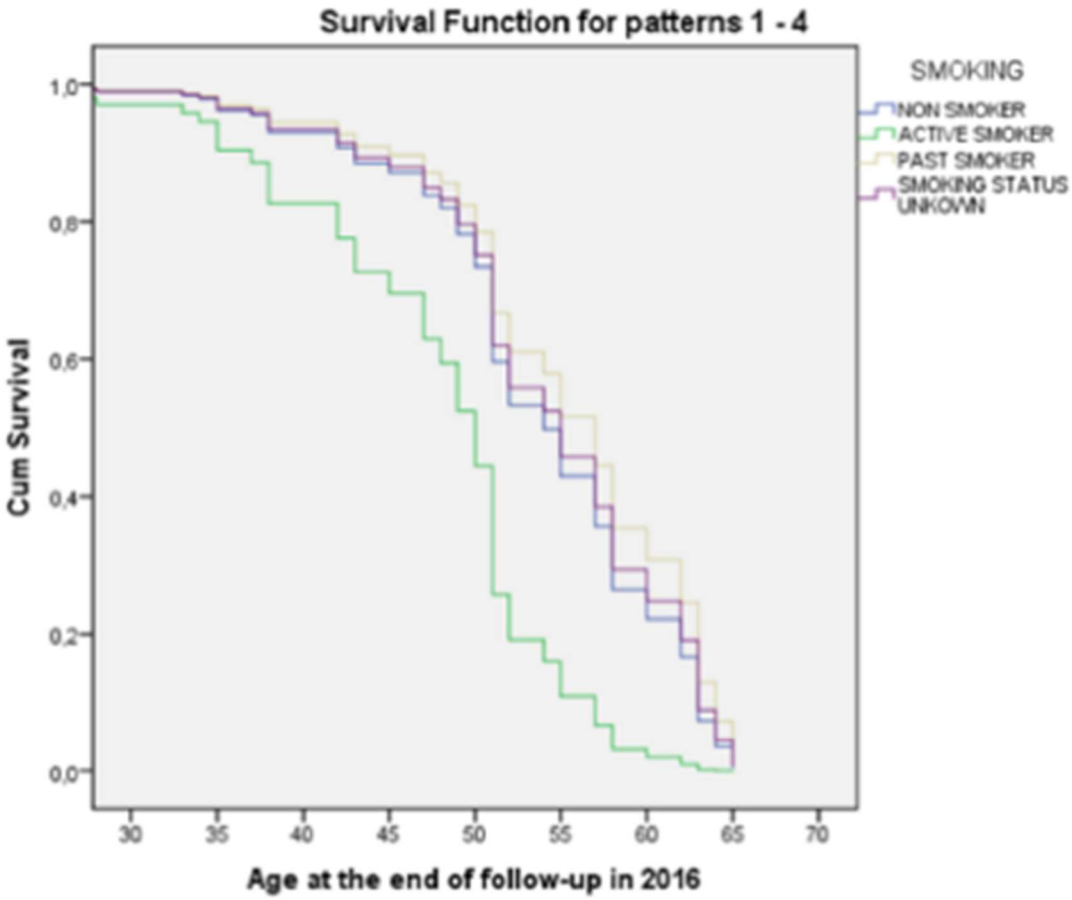

Figure 3. Survival of smokers and non-smokers from birth to endpoint of EDSS 2.5 among patients diagnosed from 1 January 2010 to 31 December 2014. (log rank p=0.121)

12.7 Disability progression in RRMS group

In the separate Cox analysis for the RRMS group (n=176) is shown in Table 3. Active smoking (p=0.047), longer diagnostic delay (p=0.000) and higher age at first symptoms (p=0.003) were statistically significantly associated with reaching the endpoint in both univariable and multivariable models. Same was true for motor (p=0.005) and multiple first symptoms (p=0.013).

Table 3: Cox model. Risk of reaching EDSS 2.5 by the end of follow up in the RRMS group (n=176).

	UNIVARIABLE			MULTIVARIABLE		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
First symptom						
Visual tract	1.0		0.088	1.0		0.073
Sensory	1.8	0.68-4.7	0.241	3.0	0.95-9.3	0.061
Motor	5.3	1.6-16.8	0.005	7.4	1.8-29.7	0.005
Brainstem	1.7	0.53-5.4	0.368	2.7	0.68-10.6	0.160
Multiple	3.5	0.89-13.5	0.074	6.6	1.5-29.0	0.013
Other	4.8	0.58-39.2	0.146	2.4	0.24-23.1	0.461
Gender						
Female	1.0			1.0		
Male	1.0	0.47-2.4	0.908	0.77	0.29-2.1	0.596
Smoking status						
No smoking	1.0		0.467	1.0		0.219
Active smoker	1.6	0.63-3.9	0.342	3.3	1.0-10.6	0.047
Past smoker	0.7	0.20-2.6	0.609	1.1	0.28-4.6	0.860
Smokig status unknown	1.7	0.68-4.2	0.265	1.5	0.52-4.4	0.444
Diagnostic delay	1.1	1.0-1.1	0.000	1.1	1.1-1.2	0.000
Age at initial symptoms	1.1	1.0-1.1	0.004	1.1	1.0-1.1	0.003
IgG index	0.95	0.48-1.9	0.874	1.4	0.64-3.1	0.402
Number of comorbidities	1.1	0.87-1.3	0.543	1.0	0.79-1.3	0.869

In this analysis, we excluded the four aggressive cases who started treatment with natalizumab and cases with unknown or study treatment.

Total of 130 cases started with a first line DMT and in 38 cases no treatment was started. The KM survival from timepoint of definite MS diagnosis to EDSS 2.5 at the end of follow up was beneficial among patients who started DMT (log rank p=0.006) (Figure 4). Mean follow-up time in DMT group was 5.9 years (5.6-6.1) and in no treatment group 5.1 years (4.5-5.7).

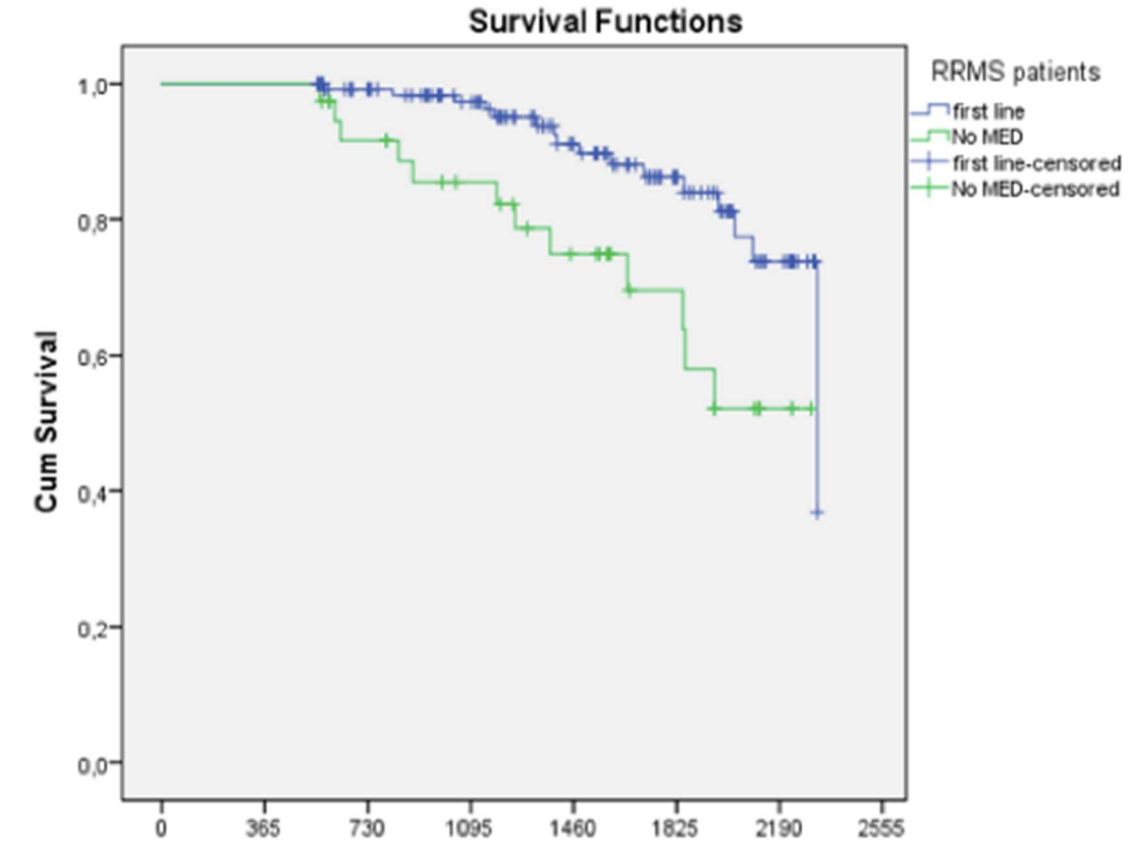

Figure 4. Survival from diagnosis to EDSS change to 2.5 or more for RRMS patients diagnosed from 1 January to 31 December 2014 with first line medication and no medication.
(log rank p=0.006)

In Cox model, the non-DMT users had a significant risk of reaching the endpoint of EDSS 2.5 by the end of follow-up in the univariable model. No risk was observed when other modulators were included in the model. The statistically significant modulators were diagnostic delay and age at onset. Results are shown in Table 4.

Table 4: Cox model. Risk of conversion to EDSS 2.5 or more up to the follow-up among cases who started treatment with first line DMT (n=130).

		UNIVARIABLE MODEL			MULTIVARIABLE MODEL		
	N	HR	95% CI	P	HR	95% CI	P
DMT use							
DMT	130	1.0					
No DMT	38	2.8	1.3-5.9	0.11	1.9	0.47-3.2	0.74
First symptom							
Visual tract	57	1.0		0.133			0.17
Sensory	54	1.0	0.38-3.2	0.86	1.6	0.52-5.3	0.46
Motor	13	4.1	1.3-13.1	0.17	5.1	1.3-19.3	0.018
Brainstem	28	1.6	0.49-5.0	0.44	1.8	0.48-6.4	0.39
Multiple	14	2.8	0.72-11.1	0.14	4.0	0.91-17.3	0.065
Other	2	3.7	0.45-30.6	0.22	2.2	0.25-19.8	0.48
Diagnostic delay (years)	168	1.1	1.0-1.1	0.000	1.2	1.1-1.2	0.001
Age at initial symptoms (years)	168	1.1	1.0-1.1	0.000	1.1	1.0-1.1	0.001

The effects of disease activity, common comorbidities and smoking in disability progression were analyzed.

In Cox regression analysis of RRMS group active smokers who had comorbidities (depression and/or diabetes) had a statistically significant risk to reach the endpoint of EDSS 2.5 (p=0.02) in univariable analysis. Active smoking doubled the risk in multivariable model when adjusted for other modifiers presented in Table 5. (HR 2.6, CI 95% 1.2-5.7, p=0.02). DMT use, comorbidities and gender showed no significant risk.

Table 5: Follow-up of the DMT group (n=130) from medication start to need for change to more efficient immunomodulatory treatment.

	UNIVARIABLE MODEL			MULTIVARIABLE MODEL		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
Age at DMT start	0.97	0.93-1.0	0.072	0.97	0.93-1.0	0.093
Time from diagnosis to first DMT	1.0	1.0-1.0	0.123	1.0	1.0-1.0	0.325
First symptom						
Visual tract	1.0		0.144	1.0		0.249
Sensory	2.2	0.88-5.3	0.092	2.3	0.92-5.6	0.077
Motor	2.6	0.75-8.8	0.131	3.0	0.86-11	0.085
Brainstem	3.8	1.4-11	0.010	3.0	1.0-8.7	0.047
Multiple or other	1.8	0.22-15	0.587	1.5	0.2-13	0.705
Gender	1.1	0.50-2.4	0.802	1.1	0.49-2.5	0.796

13 DISCUSSION

We studied the 5-year incidence and effects of DMT and several prognostic factors in MS survival up to 15 June 2016 in an incidence cohort diagnosed from 2010 to 2014 in the University Hospital of Tampere in western Finland.

The population of the Pirkanmaa district is fairly large and genetically homogenous with the rest of the Finnish population. In Finland MS patients are diagnosed by neurologists. Thus the study cohort is expected to be representative of the Finnish MS patient population. We believe that we were able to discover all new cases in the follow up time since we selected all patients who had received multiple sclerosis, morbus demyelinans or retrobulbar or optic neuritis diagnosis between 1 January 2010 and 31 December 2014 and included only the true multiple sclerosis patients who were diagnosed in the follow up period. Some of the benign cases that have initiated in the time span may have remained unnoticed due to more inconspicuous symptoms.

First of all we observed a rapid increase in incidence in a genetically stable population during a 5-year follow-up. The age-adjusted incidence has increased considerably from 6.7 per 10^5 in 1981-2010 to 10.3 per 10^5 in 2010-2014 (4). Such a rapid increase points at environmental effects and the increased hunt for MS in the presence of several immunomodulating treatments available during this period. From 2010 McDonald criteria have allowed a rapid MS diagnosis, shown also in this cohort. The mean diagnostic delay has decreased from 2.0 years before 2010 to 1.0 years in 2010-2014. This slight decrease indicates the effect of 2010 revised diagnostic criteria based mainly on magnetic resonance imaging (MRI) findings.

The age adjusted incidence was higher among women compared to men compared to the previous Finnish study (Sumelahti et al. 2014). Consistent with the earlier findings the F/M-ratio was highest in the younger age groups and the ratios were equal between genders in the older age groups (50-69 years) (Sumelahti et al. 2014). The youngest patient was 13 years old and the oldest was 68 years old at the time of diagnosis indicating a broad age spectrum in the MS patients. The demographics of the study population were consistent with earlier studies considering the distribution of PPMS and RRMS cases, female/male ratio and distribution of onset symptoms (Sumelahti et al. 2014).

In the previous Finnish study 1981-2010, 89% of patients presented with RRMS and the rest with PPMS. In the 1964-1993 study 21% of all confirmed MS patients had PPMS. In our study 92.6% were RRMS and 7.4% PPMS indicating a decreasing trend of PPMS and increasing trend of RRMS. In our study RRMS was most common in the age group of 30-39 and PPMS in the age group of 40-49. In concordance with other studies (Gholipour et al. 2011, Kantarchi and Weinshenker 2005, Levic et al. 1999) the risk of progression from diagnosis up to the end point of EDSS 2.5 for PPMS patients was significantly higher than that for RRMS patients.

Several modifiers in disease prognosis were assessed. Consistent with earlier studies multifocal and motor first symptoms, but in our multivariable Cox regression analysis also visual and sensory symptoms were associated with a worse short-term prognosis when

analyzing the incidence cohort (Gholipour et al. 2011). This is somewhat contrary to previous findings that have shown visual and sensory symptoms to be associated with a better prognosis and multifocal, motor, cerebellar and sphincter symptoms with a worse prognosis (Gholipour et al. 2011). However, in the multivariable Cox analysis for RRMS group the visual and sensory first symptoms lost their significance and only motor and multifocal symptoms were associated with a worse prognosis. This could be worth considering at the time of diagnosis of patients with multiple first symptoms or motor first symptoms. The gender was not found to be associated with a higher risk of reaching the endpoint. Higher IgG index or activity in first MRI were not found to be associated with a higher risk of reaching the EDSS 2.5 but are still important in differential diagnostics of multiple sclerosis.

The risk of progression was significantly higher if the diagnostic delay was longer or patient was older at the time of diagnosis pointing at beneficial risk among cases with a short diagnostic delay and young age at the time of diagnosis. The risk of progression to EDSS 2.5 was highest if the diagnostic delay was over ten years. This indicates that even in cases with inactive disease during the first ten years disease progresses significantly without any disease modifying treatment, the progression being faster in the later years of the disease. Benign course of MS is a controversial topic (Correale et al. 2012a, b), and eventual progression observed among cases with a slow progression at disease start favors for DMT start also in this activity subgroup.

In KM analysis whether the RRMS patient who had started a first line DMT reached the endpoint of EDSS 2.5, we found that patients who did not use any disease modifying treatment had significantly higher risk of progression to EDSS 2.5 than those who used disease modifying treatment. Since the faster progression in the group without medication is evident in such a short follow up period it would be important to prevent this disability accumulation by starting DMT early enough. The results were studied by logistic regression including several modifiers into model. In this analysis, independent survival benefit was significant among cases with a short diagnostic delay and younger age at onset, while DMT use showed no independent effect. Results points at importance of early diagnosis and related rapid start of DMT use.

In our study disease progression among active smokers was more rapid than among nonsmokers in the incidence cohort, but the difference was not statistically significant. In RRMS group active smoking showed an independent risk for disease progression when several modifiers, including common comorbidities in this cohort were included. Smoking showed a higher risk than comorbid depression and diabetes and was the most significant predictor of adverse survival, even in the presence of active immunomodulatory treatment. According to this result is essential to advise patients with MS to cease smoking. Smoking is known to be an important risk factor of multiple sclerosis and it also accelerates the disability accrual (Hawkes 2007, Healy et al. 2009, Hedström et al. 2013, Hernan et al. 2005, Riise et al. 2003). Comorbid conditions are known to decrease to quality of life in MS and may bring along life style related negative factors which should be considered in patient counseling and treatment planning. It would be important to study further the long-term effects of smoking since we were able to observe a significant survival disadvantage in such a short follow-up period indicating that smoking is a strong risk factor for faster disability accrual.

The short follow-up period allowed us to study only a short-term prognosis to the endpoint of reached EDSS 2.5. Yet we were able to observe a strongly increasing incidence of MS in the district of Pirkanmaa and several factors indicating worse prognosis. This may indicate that factors seen in long term follow up (Eriksson et al. 2003, Kantarchi and Weinshenker 2005, Runmarker and Andersen 1993) are observed also during the short-term studies, which makes follow-ups like ours meaningful today, considering the significant changes in the field on MS treatment. Strength of the study is the public healthcare which allows that all MS patients are diagnosed and treated in central or university hospitals. Patient records were carefully studied by the author and all the relevant information achievable was taken on account. However, retrospective research of the patient records may contain a reporting bias since patients tend to not report undesirable matters, such as smoking or the clinician may forget to ask or report it to the patient records. Information on depression and diagnosed diabetes may be considered reliable in this study, due to careful recording of concomitant medications observed in patient documents.

Aggressive disease course was observed in only four cases at MS onset. This was assessed by a need of second line treatment as a primary medication. These cases represent the effect of induction therapy for aggressive MS instructed in Finnish Current Care guide lines. Small number in this cohort which is less than 4-14 % reported in other studies and may be explained by the short follow up period (Menon et al. 2013). Recognition and active treatment of aggressive disease course is justified according to this notion. Early treatment start in general is supported by observation of a more benign prognosis among the DMT treated patients.

14 CONCLUSION

The ultimate goal of MS treatment is to preserve CNS functions. We found that disability progression in MS may be observed during the first five years after diagnosis and progression is significantly altered by primary progressive disease course, older age at onset, delayed diagnosis and active smoking. First line DMT use in RRMS group was related to a more beneficial survival assessed by time to reach EDSS 2.5. However, effects of rapid diagnosis and initial age showed an even stronger association to survival benefit in MS pointing at importance of early diagnosis and related start of efficient treatment. This study also points that treatment effects assessed by disability progression in majority of cases may need a longer follow-up time.

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